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(54) Title: COLON-SPECIFIC DRUG DELIVERY USING INTERPOLYMER COMPLEXATIONS

(57) Abstract: The technical field of the invention relates to pharmaceutical compositions for delivering drugs in the colon using an interpolymer complexation of a cationic polymeric glucosamine or its derivatives and an anionic, cross-linked, polyacrylic acid or its derivatives. The colon-specific drug delivery system includes (a) a core that includes a pharmaceutically active agent, a solid particulate inter-polymer complex of a cationic polymeric glucosamine or its derivatives and an anionic, cross-linked, polyacrylic acid or its derivatives; and (b) a pH-dependent coating surrounding at least a portion of the core, the pH-dependent coating being insoluble in gastric fluid and intestinal fluid below pH 6.0 but soluble in the colonic intestinal environment.



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## COLON-SPECIFIC DRUG DELIVERY USING INTERPOLYMER COMPLEXATIONS

### Field of the Invention

The technical field of the invention relates to pharmaceutical compositions for  
5 delivering drugs in the colon using an interpolymer complexation of a cationic polymeric  
glucosamine or its derivatives and an anionic, cross-linked, polyacrylic acid or its  
derivatives.

### Background of the Invention

The release of therapeutically active agents in the colon from a perorally  
10 administered dosage form is desirable in several situations. These conditions include: (1)  
topical treatment of diseases of the colon such as constipation, irritable bowel syndrome  
(IBS), Crohn's disease, ulcerative colitis, carcinomas, colorectal cancer, and infection in  
which appreciable systemic absorption of the therapeutic agent is neither required or  
desired; (2) systemic absorption of therapeutic agents such as vaccines, peptides and  
15 proteins which are subject to luminal degradation in the stomach and small intestine; and  
(3) systemic absorption of therapeutic agents for which peak systemic concentrations and  
pharmacological activity are desired at a time significantly delayed from the time of  
peroral administration. Examples of the third condition include those in which it is desired  
to administer a peroral dosage form ingested at bedtime to provide peak plasma  
20 concentration in the early morning just prior to arising. Such conditions specifically  
include, for example, nocturnal asthma, arthritis and angina. Colonic release of  
therapeutically active agents from a perorally administered dosage form necessitates that  
the release of the pharmaceutically active agent for topical activity or systemic absorption  
be prevented in the stomach and small intestine, but permitted in the colon. This in turn  
25 requires the design of the dosage form to be such that it takes advantage of features of the  
gastrointestinal tract that are specific to the colon relative to other portions of the  
gastrointestinal tract (e.g., pH).

Colon diseases include conditions such as Crohn's disease, colitis (particularly  
ulcerative colitis), irritable bowel syndrome and the like. These diseases include a  
30 spectrum of inflammatory bowel disorders with overlapping clinical, epidemiologic and  
pathologic findings but without a definite etiology. Both Crohn's disease and ulcerative  
colitis are characterized by chronic inflammation at various sites of the gastrointestinal

tract, generally the colon (i.e., that part of the intestine extending from the cecum to the rectum). In treating these disease states, it is difficult to direct drugs that are specifically anti-inflammatory in nature and act topically at the desired site.

Among the drugs for which this directed delivery may be useful includes certain  
5 glucocorticoids, amitriptyline, budesonide, mesalazine, stimulant laxatives, vaccines, peptides, antibodies, ACE inhibitors, anticholinergics, 5-HT<sub>3</sub> and 5-HT<sub>4</sub> antagonists such as alosetron and tegaserod, respectively, and other drugs such as diphenoxylate, loperamide, codeine, metronidazole, sulfasalazine, ipsalazide, balsalazide, olsalazine and mesalamine (5-amino salicylic acid). Of these compounds, particularly valuable and  
10 therefore preferred are the glucocorticoids (also known as corticosteroids), particularly for treating irritable bowel diseases (IBD) and colitis. The glucocorticoids include hydrocortisone (and pharmaceutically-acceptable salts or esters such as the acetate, cypionate, sodium phosphate, sodium succinate, butyrate, valerate, etc.), beclamethasone, beclamethasone dipropionate, betamethasone (and its pharmaceutically-acceptable salts or  
15 esters such as the benzoate, dipropionate, sodium phosphate, acetate, valerate, etc.) cortisone, cortisone acetate, dexamethasone, dexamethasone acetate, dexamethasone sodium phosphate, flunisolide, methylprednisone, methylprednisone acetate, methylprednisone sodium succinate, paramethasone acetate, prednisilone, prednisilone acetate, prednisilone sodium phosphate, prednisilone tebutate, prednisone, triamcinolone,  
20 triamcinolone acetonide, triamcinolone diacetate, triamcinolone hexacetonide, alclometasone dipropionate, amcinonide, clobetasol propionate, clocortilone pivalate, desonide, desoximetasone, diflorasone diacetate, fluocinolone acetonide, fluocinonide, fluorometholone, flurandrenolide, halcinonide, medrysone, mometasone furoate, budesonide, fluticasone, and the like.

25 The general approaches to delivering drugs to the colon include designs that are based on: 1) an enteric coating designed to release drug in the more alkaline environment of the gastrointestinal tract, 2) bioerodible coatings and matrices, 3) prodrugs, 4) timed-release systems, 5) sustained release systems that release the drug or drugs after they transit through the small intestine and reach the large intestine, 6) hydrogels and matrices,  
30 and 7) bacterial degradable polymers.

All these approaches might ensure that the dosage form remains intact and does not release the active pharmaceutical ingredient before reaching the lower intestinal tract, particularly the colon. However, because of the paucity of water in the latter parts of the

colon and the influence of spodogenous contents, among other relevant factors, the desired concentration of the active pharmaceutical ingredient may not be attained due to limited diffusion.

To obviate this problem, several water-swellaable polymers and hydrogels have  
5 been used for preparing colon-specific drug delivery systems. These absorb water present in the colon, as a result of which the matrix swells and releases the drug through diffusion. However, due to there being less water present in the colon, the extent of swelling is not very satisfactory and consequently most of the drug remains entrapped in the dosage form and is ultimately excreted. Moreover, these swollen hydrogels and polymers may lose  
10 their structural integrity during the colonic transit.

Therefore, there is a need for substances that can swell significantly in the presence of less water and maintain its structural integrity during colonic transit. One such substance is a solid, particulate complex formed by the inter-polymer complexation of a cationic polymeric glucosamine or its derivatives and an anionic, cross-linked, polyacrylic  
15 acid or its derivatives as disclosed in our copending application PCT/IB02/01708.

#### Summary of the Invention

In one general aspect there is provided a colon-specific drug delivery system that includes (a) a core that includes a pharmaceutically active agent, a solid particulate inter-polymer complex of a cationic polymeric glucosamine or its derivatives and an anionic,  
20 cross-linked, polyacrylic acid or its derivatives; and (b) a pH-dependent coating surrounding at least a portion of the core, the pH-dependent coating being insoluble in gastric fluid and intestinal fluid below pH 6.0 but soluble in the colonic intestinal environment.

Embodiments of the drug delivery system may include one or more of the  
25 following features. For example, the colon-specific drug delivery system may further include one or more sustained release materials in or around the core.

The pharmaceutically active ingredient may be one or more of glucocorticoids, amitriptyline, budesonide, mesalazine, stimulant laxatives, vaccines, peptides, antibodies, ACE inhibitors, anticholinergics, 5-HT<sub>3</sub> antagonists, 5-HT<sub>4</sub> antagonists, alosetron,  
30 tegaserod, diphenoxylate, loperamide, codeine, metronidazole, sulfasalazine, ipsalazide, balsalazide, olsalazine and mesalamine (5-amino salicylic acid).

Suitable glucocorticoids may be one or more of beclamethasone, beclamethasone dipropionate, betamethasone and its pharmaceutically-acceptable salts or esters, cortisone, cortisone acetate, dexamethasone, dexamethasone acetate, dexamethasone sodium phosphate, flunisolide, methylprednisone, methylprednisone acetate, methylprednisone sodium succinate, paramethasone acetate, prednisilone, prednisilone acetate, prednisilone sodium phosphate, prednisilone tebutate, prednisone, triamcinolone, triamcinolone acetonide, triamcinolone diacetate, triacsinilone hexacetonide, alclometasone dipropionate, amcinonide, clobetasol propionate, clocortilone pivalate, desonide, desoximetasone, diflorasone diacetate, fluocinolone acetonide, fluocinonide, fluorometholone, flurandrenolide, halcinonide, medrysone, mometasone furoate, budesonide, and fluticasone.

The glucosamine may be one or more of 2-amino-2-deoxy- $\alpha$ -D-glucose, chitosan, poly-[1-4]- $\beta$ -D-glucosamine, a partially deacetylated chitin, carboxymethyl chitosan, hydroxypropyl chitosan, and glycol chitosan. The glucosamine may be acid soluble. The glucosamine may have at least about a 75% degree of acetylation, or at least about an 85% degree of acetylation.

The anionic cross-linked polyacrylic acid or its derivatives may be a water-swellaable, high molecular weight, cross-linked homopolymers and/or copolymers that form a hydrogel in an aqueous media. The anionic cross-linked polyacrylic acid or its derivatives may be a cross-linked methacrylic acid, and may be one or more of (i) homopolymers of acrylic acid cross-linked with allyl sucrose or allyl pentaerythritol (Carbopol homopolymers), (ii) homopolymers of acrylic acid cross-linked with divinyl glycol (Noveon polycarbophils), and (iii) copolymers of acrylic acid with minor levels of long chain alkyl acrylate co-monomers cross-linked with allylpentaerythritol (Carbopol copolymers and Pemulen polymeric emulsifiers). The homopolymers of acrylic acid cross-linked with allyl sucrose or allyl pentaerythritol polymer may have a molecular weight of between 700,000 and 4,000,000,000. The homopolymers of acrylic acid cross-linked with allyl sucrose or allyl pentaerythritol polymer may swell in water up to 1000 times its original volume to form a gel when exposed to a pH environment above 6. The homopolymers of acrylic acid cross-linked with allyl sucrose or allyl pentaerythritol polymer may have carboxylate groups on the polymer backbone that ionize and provide repulsion between the negative particles.

The sustained release material may be a material that sustains or delays the release of the active pharmaceutical ingredient from the dosage form. The sustained release material may be one or more of hydrophilic polymers, digestible long chain substituted or unsubstituted hydrocarbons, polyalkylene glycols, and hydrophobic polymers. The hydrophilic polymers may be one or more of gums, cellulose ethers, acrylic resins and protein derived materials. The digestible long chain substituted or unsubstituted hydrocarbons may be one or more of fatty acids, fatty alcohols, glyceryl esters of fatty acids, mineral and vegetable oils and waxes. The hydrophobic polymers may be one or more of water-insoluble cellulose polymers, acrylic acid and methacrylic acid copolymers, and methacrylic acid copolymers.

The pH-dependent coating may be one or more of a cellulose acetate trimellitate (CAT), hydroxypropylmethyl cellulose phthalate (HPMCP), polyvinyl acetate phthalate (PVAP), cellulose acetate phthalate (CAP) and shellac, methylmethacrylates or copolymers of methacrylic acid and ethylmethacrylate. The active ingredient may be present at between about 40% w/w and 60% w/w of the drug delivery system.

The interpolymer complex of a cationic polymeric glucosamine or its derivatives and an anionic, cross-linked, polyacrylic acid or its derivatives may be present at between about 20% w/w and about 40% w/w of the drug delivery system.

The drug delivery system may be one or more of beads, spheroids, microspheres, seeds, pellets, multi-particulate systems, matrix-drug tablets, tablets prepared by compression, free matrix-drug pellets, matrix-drug pellets that are packed in gelatin capsules, free matrix-drug micro particles, matrix-drug micro particles packed in gelatin capsules, and multi-layered tablets that include a drug core coated with one or more biodegradable polymers.

The drug delivery system may be provided for topical treatment of diseases of the colon. The diseases of the colon may be one or more of constipation, irritable bowel syndrome (IBS), Crohn's disease, ulcerative colitis, carcinomas, colorectal cancer, and an infection in which appreciable systemic absorption of the therapeutic agent is neither required nor desired.

The drug delivery system may be provided for systemic absorption of therapeutic agents that are subject to luminal degradation in the stomach and/or the small intestine. The therapeutic agents may be one or more of peptides and proteins.

The drug delivery system may be provided for systemic absorption of therapeutic agents for conditions in which the peak systemic concentrations and pharmacological activity are desired at a time significantly delayed from the time of peroral administration. The condition may be one or more of nocturnal asthma, arthritis and angina.

5 In another general aspect there is provided a method of colon-specific drug delivery. The method includes administering a drug delivery system intended for oral administration to treat a medical condition, the drug delivery system including (a) a core that includes a pharmaceutically active agent, a solid particulate inter-polymer complex of a cationic polymeric glucosamine or its derivatives and an anionic, cross-linked,  
10 polyacrylic acid or its derivatives; and (b) a pH-dependent coating surrounding at least a portion of the core, the pH-dependent coating being insoluble in gastric fluid and intestinal fluid below pH 6.0 but soluble in the colonic intestinal environment.

Embodiments of the method of delivery may include one or more of the above features or the following features. For example, the drug delivery system may further  
15 include one or more sustained release materials in or around the core.

The details of one or more embodiments of the inventions are set forth in the description below. Other features, objects and advantages of the inventions will be apparent from the description and claims.

#### Detailed Description of the Invention

20 As can be seen from the prior art discussed above, there is a need for substances that can swell significantly in the presence of the reduced amount of water present in the surroundings of the colon and maintain its structural integrity during the colonic transit. As described in more detail herein, the inventors have developed such a drug delivery system that is based on a solid, particulate complex formed by the interpolymer  
25 complexation of a cationic polymeric glucosamine or its derivatives and an anionic, cross-linked, polyacrylic acid or its derivatives.

Glucosamine, which is formed in the body as glucosamine 6-phosphate, is 2-amino-2-deoxy- $\alpha$ -D-glucose. It is one of the two hexosamine sugars (6 carbon amino sugars) common in animal cells. Structurally, glucosamine is modified glucose with a  
30  $\text{NH}_3$ -group replacing the OH-group found on carbon two (C-2). A glucosamine that is of particular relevance to this application is chitosan. Chitosan is poly-[1-4]- $\beta$ -D-glucosamine and is a partially deacetylated chitin. As referred to herein, it is acid soluble

and has at least about a 75% degree of acetylation, more preferably, the degree of acetylation is in excess of about 85%. Other suitable glucosamines include, but are not limited to, carboxymethyl chitosan, hydroxypropyl chitosan and glycol chitosan.

- Cross-linked polyacrylic acid or its derivatives, as referred to in this application, include water-swellaable, high molecular weight, cross-linked homopolymers and copolymers, which form hydrogels in aqueous media. The crosslinker types and levels can be modified, with regard to amounts and characteristics of the hydrophobic co-monomers. Commercial grades of cross-linked methacrylic acid are available from Noveon (formerly, BF Goodrich) as Carbopol®, Pemulen®, and Noveon resins.
- Specifically, the resins are: (i) homopolymers of acrylic acid cross-linked with allyl sucrose or allyl pentaerythritol (Carbopol homopolymers), (ii) homopolymers of acrylic acid cross-linked with divinyl glycol (Noveon polycarbophils), and (iii) copolymers of acrylic acid with minor levels of long chain alkyl acrylate co-monomers cross-linked with allylpentaerythritol (Carbopol copolymers and Pemulen polymeric emulsifiers).
- Carbopol® and Pemulen® polymers are described in detail in the Handbook of Pharmaceutical Excipients, fourth edition, which is incorporated herein in its entirety by reference.

The molecular weight of carbopol polymers is theoretically estimated to range from 700,000 to 3 or 4 billion. They swell in water up to 1000 times their original volume to form a gel when exposed to a pH environment above 6. Since the pKa of these polymers is  $6 \pm 0.5$ , the carboxylate groups on the polymer backbone ionize, resulting in repulsion between the negative particles, which adds to the swelling of the polymer. Cross-linked polymers do not generally dissolve in water.

The inventors have formulated a colon-specific drug delivery system (CSDDS), using the inter-polymer complex of a cationic polymeric glucosamine or its derivatives and an anionic, cross-linked, polyacrylic acid or its derivatives. The CSDDS includes: (1) a core that includes a pharmaceutically active agent, a solid particulate inter-polymer complex of a cationic polymeric glucosamine or its derivatives and an anionic, cross-linked, polyacrylic acid or its derivatives, and may contain a sustained release matrix material, and (2) a pH-dependent coating which is insoluble in gastric fluid and intestinal fluid below pH 6.0 but soluble in colonic intestinal environment.



The pH-dependent coating ensures that the dosage form remains intact before reaching the lower regions of ileum and/or the ascending colon and no release occurs in the gastric region and upper regions of small intestine. When the dosage form reaches the lower regions of the ileum and/or the ascending colon, the pH-dependent coating starts dissolving and the water present in the surroundings enters the dosage form. On coming in contact with water, the interpolymer complex dispersed in the matrix imbibes it and starts swelling. Some of the examples and embodiments developed during the course of invention exhibited a particular phenomenon, which has been termed as the "Sesame bun phenomenon".

According to this phenomenon, as the interpolymer complex starts to swell, the active and the sustained release matrix material get slowly pushed towards the periphery of the dosage form, which consequently takes the shape of a swollen roll ("bun"). Gradually all the active and the sustained release material are concentrated at the periphery, giving it an appearance much like sesame seeds spread all over a bun. This is advantageous due to at least the following reasons:

1. The water present in the swollen interpolymer complex is used for drug release from the sustained release matrix by diffusion, particularly in the transverse and descending colon where there is very little or no water, and
2. Since the active pharmaceutical ingredient is in close proximity to the inner walls of the colon, the length of the path traveled before diffusion (i.e., the diffusion path) is reduced and therefore this will in turn enhance the local contact of the drug with affected tissues as well as possibly provide enhanced drug absorption.

The polymer coating materials are selected such that the pharmaceutically active ingredient will be released at about the time that the dosage form reaches the inlet between the small intestine and the colon, or thereafter in the colon. The selection is based upon the pH profile of the small intestine and colon. The pH of the small intestine gradually increases from about 5 to 5.5 in the duodenum to about 7.2 in the distal portions of the small intestine (ileum). In order to provide a predictable dissolution time corresponding to the small intestinal transit time of about 3 hours and permit reproducible release of drug at the inlet between the small intestine and the colon, or thereafter in the colon, the coating should begin to dissolve within the pH range of the small intestine and continue to

dissolve at the pH of the proximal colon. Suitable coating materials are those which dissolve at a pH of 5 or above. The coatings therefore only begin to dissolve when they have left the stomach and entered the small intestine. Such a coating can be made from a variety of polymers such as cellulose acetate trimellitate (CAT), hydroxypropylmethyl  
5 cellulose phthalate (HPMCP), polyvinyl acetate phthalate (PVAP), cellulose acetate phthalate (CAP) and shellac, methylmethacrylates or copolymers of methacrylic acid and ethylmethacrylate. Particularly, methacrylates are used. Such materials are available as Eudragit® polymers (Rohm Pharma, Darmstadt, Germany).

Eudragits are copolymers of methacrylic acid and methylmethacrylate.

10 Compositions based on Eudragit L100 and Eudragit S100 are particularly utilized.

Eudragit L100 dissolves at  $\text{pH} \geq 6$  and comprises 48.3% methacrylic acid units per g dry substance; Eudragit S100 dissolves at  $\geq \text{pH} 7$  and comprises 29.2% methacrylic acid units per g dry substance.

Eudragit L, is an anionic copolymer derived from methacrylic acid and methyl  
15 methacrylate, with a ratio of free carboxyl groups to the ester groups of approximately 1:1, and a mean molecular weight of approximately 135,000, from Rohm Tech. Eudragit S is an anionic copolymer derived from methacrylic acid and methyl methacrylate, with a ratio of free carboxyl groups to the ester groups of approximately 1:2, and a mean molecular weight of approximately 135,000, from Rohm Tech.

20 The total amount of enteric polymer coatings on the dosage form must be sufficient such that complete dissolution of the coating does not occur until the dosage form is at a location within the gastrointestinal tract near the opening to, or within the colon, thereby releasing the active ingredient in the colon.

The enteric polymer coating material may be applied to the core as a solution in a  
25 pharmaceutically acceptable solvent such as ethanol, acetone, isopropanol, ethyl acetate, or mixtures thereof; as an aqueous solution buffered with ammonium hydroxide; or as a fine dispersion in water using any number of processes known to one skilled in the art, including but not limited to, perforated pan coating and fluid bed coating.

To enhance the elasticity of the coating materials, preferably the coating material  
30 of the present invention also comprises a plasticizer. Appropriate plasticizers include polyethylene glycols, propylene glycols, dibutyl phthalate, diethyl phthalate, tributyl citrate, butyl glycolate, triacetin, castor oil and citric acid esters; particularly the plasticizer

is dibutyl phthalate or triethyl citrate. These plasticizers are present in an amount to facilitate the coating process and to obtain an even coating film with enhanced physical stability.

In addition, to facilitate the coating process, the coating material may also  
5 comprise inert solid particulates. Suitable inert solid particulates include talc and titanium dioxide. The selections of plasticizer, inert solid particulate, and levels thereof, solvent and process are based upon the specific enteric polymer used and the type of dosage form used according to criteria known to those skilled in the art.

The Handbook of Pharmaceutical Excipients, fourth edition, provides details on  
10 the Eudragit polymers, and is incorporated herein in its entirety by reference.

The sustained release material employed may be any material that sustains or delays the release of the active pharmaceutical ingredient from the dosage form. Suitable materials for inclusion in a sustained-release matrix include one or more of:

- 15 (a) Hydrophilic polymers, such as gums, cellulose ethers, acrylic resins and protein derived materials,
- (b) Digestible, long chain substituted or unsubstituted hydrocarbons, such as fatty acids, fatty alcohols, glyceryl esters of fatty acids, mineral and vegetable oils and waxes,
- (c) Polyalkylene glycols, and
- 20 (d) Hydrophobic polymers including but not limited to water-insoluble cellulose polymers, acrylic acid and methacrylic acid copolymers, methacrylic acid copolymers.

The CSDDS may be formed as beads, spheroids, microspheres, seeds, pellets, and other multi-particulate systems. Specific embodiments of prepared formulations of the  
25 compositions of the invention, include, for example, matrix-drug tablets, especially tablets prepared by compression; matrix-drug pellets, either free or packed in gelatin capsules, or any other means allowing oral administration; matrix-drug micro-particles, either free or packed in gelatin capsules or any other means allowing oral administration; and multi-layered tablets which comprise a drug core, coated with biodegradable polymers, the  
30 polymeric layer being prepared, for example, by spray-coating, molding or double-press procedure. All of these techniques for preparation of such formulations are well known in the art.

Some representative examples are provided below to exemplify the inventions but are not intended to be construed to be limiting of the inventions.

**EXAMPLE 1**

Sustained release formulation of mesalamine for colon-specific drug delivery systems

5

S.No.	Ingredients	% w/w (approx.)
1.	Mesalamine	49.4
2.	Microcrystalline cellulose	12.35
3.	Eudragit RS 30D	12.35
4.	Triethylcitrate	1.24
5.	Interpolymer complex of a cationic polymeric glucosamine or its derivatives and an anionic, cross-linked, polyacrylic acid or its derivatives	24.7

**Process:**

1. Mesalamine and microcrystalline cellulose were accurately weighed and blended uniformly.
2. Eudragit RS 30D and triethylcitrate were separately blended to form a colloidal solution.
3. The blend of step 1 was granulated with the colloidal solution of step 2.
4. The wet mass of step 3 was sifted and dried at 60°C for 10 minutes.
5. The inter-polymer complex was added to the semi-dried granules of step 4 and uniformly mixed.
6. The granules obtained in step 5 were dried at 70°C for about 18 hours.
7. The dried granules of step 6 were sifted and filled into capsules.
8. The capsules were finally coated with a coating solution prepared according to the procedure described below.

**Composition of the Coating Solution****Coating solution I**

	<b>Ingredients</b>	<b>% w/w (approx.)</b>
A	Eudragit L100	10
	Triethyl citrate	5
	Sodium hydroxide (1 N)	3.4
	Water	33.4
B	Talc	3.3
	Water	44.9

**Process:**

1. Part A: Eudragit L 100 was dispersed in water. To this sodium hydroxide was added slowly with stirring and the stirring was continued for 2 hours. Triethylcitrate was added gradually with continuous stirring.
2. Part B: Talc was finely dispersed in water.
3. The dispersion of Part A was gradually added to the dispersion of Part B with stirring.

## Coating solution II

	Ingredients	% w/w (approx.)
A	Eudragit S100	10
	Triethyl citrate	5
	Sodium hydroxide (1 N)	5.1
	Water	29.9
B	Talc	3.3
	Water	46.6

## Process:

- 5 1. Part A: Eudragit S 100 was dispersed in water. To this sodium hydroxide was added slowly with stirring and the stirring was continued for 2 hours. Triethylcitrate was added gradually with continuous stirring.
2. Part B: Talc was finely dispersed in water.
3. The dispersion of Part A was gradually added to the dispersion of Part B with stirring.
- 10 For coating the capsules of Example 1, coating solutions I and II were used in a ratio of 1:3.

**EXAMPLE 2**

Sustained release formulation of mesalamine for colon-specific drug delivery systems

S.No.	Ingredients	% w/w (approx.)
a.	Mesalamine	44
b.	Microcrystalline cellulose	11
c.	Eudragit RS 30D	11
d.	Triethylcitrate	1.1
e.	Interpolymer complex of a cationic polymeric glucosamine or its derivatives and an anionic, cross-linked, polyacrylic acid or its derivatives	33

15

Process: Same as described in Example 1.

The capsules obtained were coated with a coating solution prepared according to the procedure described in Example 1.

The release profiles of capsules prepared according to Examples 1 and 2 and those prepared without the interpolymer complex are provided in Table 1.

5      **Table 1: Release profiles of the capsules of Examples 1 and 2 and those prepared without the interpolymer complex in pH 7.5 phosphate buffer / 900ml/USP Apparatus II/100 rpm/37°C.**

<b>Time (hours)</b>	<b>Percent drug released from capsules of Ex. 1 (%)</b>	<b>Percent drug released from capsules of Ex. 2 (%)</b>	<b>Percent drug released from capsules prepared without the interpolymer complex (%)</b>
1.0	59.9	51.67	40.04
2.0	78.7	72.1	55.85
4.0	96.8	90.15	74.33
6.0	-	98.8	86.2

10      While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are included within the scope of the present invention.

## WE CLAIM:

- 1           1.     A colon-specific drug delivery system comprising:  
2                 a core comprising a pharmaceutically active agent, a solid particulate interpolymer  
3                 complex of a cationic polymeric glucosamine or its derivatives and an anionic, cross-  
4                 linked polyacrylic acid or its derivatives; and  
5                 a pH-dependent coating surrounding at least a portion of the core, the pH-  
6                 dependent coating being insoluble in gastric fluid and intestinal fluid below pH 6.0 but  
7                 soluble in the colonic intestinal environment.
- 1           2.     The colon-specific drug delivery system of claim 1, further comprising one  
2                 or more sustained release materials in or around the core.
- 1           3.     The colon-specific drug delivery system of claim 1, wherein the  
2                 pharmaceutically active ingredient comprises one or more of glucocorticoids,  
3                 amitriptyline, budesonide, mesalazine, stimulant laxatives, vaccines, peptides, antibodies,  
4                 ACE inhibitors, anticholinergics, 5-HT<sub>3</sub> antagonists, 5-HT<sub>4</sub> antagonists, alosetron,  
5                 tegaserod, diphenoxylate, loperamide, codeine, metronidazole, sulfasalazine, ipsalazide,  
6                 balsalazide, olsalazine and mesalamine (5-amino salicylic acid).
- 1           4.     The colon-specific drug delivery system of claim 3, wherein the  
2                 glucocorticoids comprise one or more of beclamethasone, beclamethasone dipropionate,  
3                 betamethasone and its pharmaceutically-acceptable salts or esters, cortisone, cortisone  
4                 acetate, dexamethasone, dexamethasone acetate, dexamethasone sodium phosphate,  
5                 flunisolide, methylprednisone, methylprednisone acetate, methylprednisone sodium  
6                 succinate, paramethasone acetate, prednisilone, prednisilone acetate, prednisilone sodium  
7                 phosphate, prednisilone tebutate, prednisone, triamcinolone, triamcinolone acetonide,  
8                 triamcinolone diacetate, triamcinolone hexacetonide, alclometasone dipropionate,  
9                 amcinonide, clobetasol propionate, clocortilone pivalate, desonide, desoximetasone,  
10                diflorasone diacetate, fluocinolone acetonide, fluocinonide, fluorometholone,  
11                flurandrenolide, halcinonide, medrysone, mometasone furoate, budesonide, and  
12                fluticasone.
- 1           5.     The colon-specific drug delivery system of claim 1, wherein the  
2                 glucosamine comprises one or more of 2-amino-2-deoxy- $\alpha$ -D-glucose, chitosan, poly-  
3                 [1-4]- $\beta$ -D-glucosamine, a partially deacetylated chitin, carboxymethyl chitosan,  
4                 hydroxypropyl chitosan, and glycol chitosan.



1           6.     The colon-specific drug delivery system of claim 1, wherein the  
2 glucosamine is acid soluble.

1           7.     The colon-specific drug delivery system of claim 1, wherein the  
2 glucosamine has at least about a 75% degree of acetylation.

1           8.     The colon-specific drug delivery system of claim 1, wherein the  
2 glucosamine has at least about an 85% degree of acetylation.

1           9.     The colon-specific drug delivery system of claim 1, wherein the anionic  
2 cross-linked polyacrylic acid or its derivatives comprises one or more water-swella-  
3 ble, high molecular weight, cross-linked homopolymers and/or copolymers that form a  
4 hydrogel in an aqueous media.

1           10.    The colon-specific drug delivery system of claim 1, wherein the anionic  
2 cross-linked polyacrylic acid or its derivatives comprises a cross-linked methacrylic acid.

1           11.    The colon-specific drug delivery system of claim 1, wherein the anionic  
2 cross-linked polyacrylic acid or its derivatives comprise one or more of (i) homopolymers  
3 of acrylic acid cross-linked with allyl sucrose or allyl pentaerythritol, (ii) homopolymers  
4 of acrylic acid cross-linked with divinyl glycol, and (iii) copolymers of acrylic acid with  
5 minor levels of long chain alkyl acrylate co-monomers cross-linked with  
6 allylpentaerythritol.

1           12.    The colon-specific drug delivery system of claim 11, wherein the  
2 homopolymers of acrylic acid cross-linked with allyl sucrose or allyl pentaerythritol has a  
3 molecular weight of between 700,000 and 4,000,000,000.

1           13.    The colon-specific drug delivery system of claim 11, wherein the  
2 homopolymers of acrylic acid cross-linked with allyl sucrose or allyl pentaerythritol  
3 polymer swell in water up to 1000 times its original volume to form a gel when exposed to  
4 a pH environment above 6.

1           14.    The colon-specific drug delivery system of claim 11, wherein the  
2 homopolymers of acrylic acid cross-linked with allyl sucrose or allyl pentaerythritol  
3 polymer comprise carboxylate groups on the polymer backbone that ionize and provide  
4 repulsion between the negative particles.

1           15.    The colon-specific drug delivery system of claim 2, wherein the sustained  
2 release material comprises a material that sustains or delays the release of the active  
3 pharmaceutical ingredient from the dosage form.

1           16.    The colon-specific drug delivery system of claim 2, wherein the sustained  
2 release material comprises one or more of hydrophilic polymers, digestible long chain  
3 substituted or unsubstituted hydrocarbons, polyalkylene glycols, and hydrophobic  
4 polymers.

1           17.    The colon-specific drug delivery system of claim 16, wherein the  
2 hydrophilic polymers comprise one or more of gums, cellulose ethers, acrylic resins and  
3 protein derived materials.

1           18.    The colon-specific drug delivery system of claim 16, wherein the digestible  
2 long chain substituted or unsubstituted hydrocarbons comprise one or more of fatty acids,  
3 fatty alcohols, glyceryl esters of fatty acids, mineral and vegetable oils and waxes.

1           19.    The colon-specific drug delivery system of claim 16, wherein the  
2 hydrophobic polymers comprise one or more of water-insoluble cellulose polymers,  
3 acrylic acid and methacrylic acid copolymers, and methacrylic acid copolymers.

1           20.    The colon-specific drug delivery system of claim 1, wherein the pH-  
2 dependent coating comprises one or more of cellulose acetate trimellitate (CAT),  
3 hydroxypropylmethyl cellulose phthalate (HPMCP), polyvinyl acetate phthalate (PVAP),  
4 cellulose acetate phthalate (CAP) and shellac, methylmethacrylates or copolymers of  
5 methacrylic acid and ethylmethacrylate.

1           21.    The colon-specific drug delivery system of claim 1, wherein the active  
2 ingredient comprises between about 40% w/w and 60% w/w of the drug delivery system.

1           22.    The colon-specific drug delivery system of claim 1, wherein the  
2 interpolymer complex of a cationic polymeric glucosamine or its derivatives and an  
3 anionic, cross-linked polyacrylic acid or its derivatives comprises between about 20% w/w  
4 and about 40% w/w.

1           23.    The colon-specific drug delivery system of claim 1, wherein the drug  
2 delivery system comprises one or more of beads, spheroids, microspheres, seeds, pellets,  
3 multi-particulate systems, matrix-drug tablets, tablets prepared by compression, free  
4 matrix-drug pellets, matrix-drug pellets that are packed in gelatin capsules, free matrix-

5 drug micro-particles, matrix-drug micro-particles packed in gelatin capsules, and multi-  
6 layered tablets that comprise a drug core coated with one or more biodegradable polymers.

1 24. The colon-specific drug delivery system of claim 1, wherein the drug  
2 delivery system is provided for topical treatment of diseases of the colon.

1 25. The colon-specific drug delivery system of claim 24, wherein the topical  
2 treatment of diseases of the colon comprises one or more of constipation, irritable bowel  
3 syndrome (IBS), Crohn's disease, ulcerative colitis, carcinomas, colorectal cancer, and an  
4 infection in which appreciable systemic absorption of the therapeutic agent is neither  
5 required nor desired.

1 26. The colon-specific drug delivery system of claim 1, wherein the drug  
2 delivery system is provided for systemic absorption of therapeutic agents that are subject  
3 to luminal degradation in the stomach and/or the small intestine.

1 27. The colon-specific drug delivery system of claim 26, wherein the  
2 therapeutic agents comprise one or more of peptides and proteins.

1 28. The colon-specific drug delivery system of claim 1, wherein the drug  
2 delivery system is provided for systemic absorption of therapeutic agents for conditions in  
3 which the peak systemic concentrations and pharmacological activity are desired at a time  
4 significantly delayed from the time of peroral administration.

1 29. The colon-specific drug delivery system of claim 28, wherein the condition  
2 comprises one or more of nocturnal asthma, arthritis and angina.

1 30. A method of colon-specific drug delivery, the method comprising:

2 administering a drug delivery system for oral administration to treat a medical  
3 condition, the drug delivery system comprising

4 a core comprising a pharmaceutically active agent, a solid particulate inter-  
5 polymer complex of a cationic polymeric glucosamine or its derivatives and an  
6 anionic, cross-linked polyacrylic acid or its derivatives; and

7 a pH-dependent coating surrounding at least a portion of the core, the pH-  
8 dependent coating being insoluble in gastric fluid and intestinal fluid below pH 6.0  
9 but soluble in the colonic intestinal environment.

- 1           31.     The method of colon-specific drug delivery of claim 30, wherein the drug  
2     delivery system further comprises one or more sustained release materials in or around the  
3     core.

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/IB2004/003114

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K9/16 A61K9/28 A61K31/60

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BIOSIS, EMBASE

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 03/068843 A (WILSON CLIVE ; MUKHERJI GOUR (IN); RANBAXY LAB LTD (IN); RAMPAL ASHOK) 21 August 2003 (2003-08-21) cited in the application page 9, lines 19-22; claim 1	1-31
Y	EP 1 203 590 A (DAINIPPON PHARMACEUTICAL CO) 8 May 2002 (2002-05-08) paragraphs '0022!, '0031!, '0033!; claim 1	1-31

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

\* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

18 January 2005

Date of mailing of the international search report

28/01/2005

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# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/IB2004/003114

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DE LA TORRE P M ET AL: "Interpolymer complexes of poly(acrylic acid) and chitosan: influence of the ionic hydrogel-forming medium" BIOMATERIALS, ELSEVIER SCIENCE PUBLISHERS BV., BARKING, GB, vol. 24, no. 8, April 2003 (2003-04), pages 1459-1468, XP004401479 ISSN: 0142-9612 the whole document	1-31
P, A	WO 03/097714 A (WILSON CLIVE ; MUKERJEE GOUR (IN); RAVIKUMAR N (IN); RAMPAL ASHOK (IN)) 27 November 2003 (2003-11-27) page 7, lines 1-18; claim 1	1-31

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/IB2004/003114

### Box II Observations where certain claims were found unsearchable (Continuation of Item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 30, 31  
because they relate to subject matter not required to be searched by this Authority, namely:  
Although claims 30 and 31 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

### Box III Observations where unity of invention is lacking (Continuation of Item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.  
☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No.

PCT/IB2004/003114

Patent document cited in search report		Publication date		Patent family member(s)	Publication date
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			WO	03097714 A1	27-11-2003